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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/955,572	10/22/97	KWON B	IND4-D11B

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EXAMINER
KAUFMAN, C

ART UNIT	PAPER NUMBER
1646	18

DATE MAILED: 11/23/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Advisory Action

Application No.	Applicant(s)
08/955,572	Kwon
Examiner	**Group Art Unit**
Claire M. Kaufman	1646

THE PERIOD FOR RESPONSE: [check only a) or b)]

a) ☐ expires _____ months from the mailing date of the final rejection.

b) ☐ expires either three months from the mailing date of the final rejection, or on the mailing date of this Advisory Action, whichever is later. In no event, however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition, and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☒ Appellant's Brief is due two months from the date of the Notice of Appeal filed on *Oct 30, 1998* (or within any period for response set forth above, whichever is later). See 37 CFR 1.191(d) and 37 CFR 1.192(a).

Applicant's response to the final rejection, filed on *Oct 30, 1998* has been considered with the following effect, but is NOT deemed to place the application in condition for allowance:

☒ The proposed amendment(s):

☐ will be entered upon filing of a Notice of Appeal and an Appeal Brief.

☒ will not be entered because:

☒ they raise new issues that would require further consideration and/or search. (See note below).

☐ they raise the issue of new matter. (See note below).

☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

☐ they present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE: *The claiming of non-specified "fragments" would require a new search.*

☐ Applicant's response has overcome the following rejection(s):

☐ Newly proposed or amended claims _____ would be allowable if submitted in a separate, timely filed amendment cancelling the non-allowable claims.

☒ The affidavit, exhibit or request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See attachment.

☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

☒ For purposes of Appeal, the status of the claims is as follows (see attached written explanation, if any):

Claims allowed: _____

Claims objected to: _____

Claims rejected: *5, 6, 21, and 24-26*

☐ The proposed drawing correction filed on _____ ☐has ☐has not been approved by the Examiner.

☐ Note the attached Information Disclosure Statement(s), PTO-1449, Paper No(s). _____ .

☒ Other *the substitute sequence listing has not been entered because it was not accompanied by a statement that the paper and computer readable copies are the same and introduce no new matter. See MPEP 2426.*

CONTINUATION OF ADVISORY ACTION--PAPER #18

Response to Arguments

Claim Rejections - 35 USC § 112

1. Applicant argues that by knowing that amino acids 1-186 of H4-1BB contain the signal sequence and the entire extracellular domain of H4-1BB (page 16 of the specification), provides sufficient guidance to prepare other constructs encoding portions of the extracellular domain of H4-1BB, particularly fragments which bind 4-1BB ligand. This is not persuasive for the reasons that the construct described on page 16 of the specification comprises the signal sequence and extracellular domain, but which portion is the extracellular domain is not disclosed, nor is it disclosed what portion of the extracellular domain is required for binding (see for example, Office action of paper #7, section 22). The disclosure of the current application in combination with knowledge from the prior art is not sufficient to enable a fragment which binds a ligand when what is provided is a region of a protein comprising an extracellular domain which would reasonably be expected to bind a ligand, no identification of the ligand binding domain in the prior art for a 4-1BB protein, a lack of a specific ligand, and knowledge that the full-length H4-1BB protein binds B cells and not T cells, without knowing what on the B cells it binds. For the reasons presented in the previous Office actions, it would require undue experimentation to practice the claimed invention.

Applicant argues that knowledge generally available in the art combined with the full-length sequence of SEQ ID NO:2, which is a receptor, enables a fragment which bind to a cell membrane ligand. This argument is not persuasive for the reasons above and because applicants did not disclose either the binding domain of SEQ ID NO:2 nor the ligand which binds it. The claims provide an invitation to experiment; and, because of the lack of examples, guidance about which residues are necessary for binding, breadth of the claims (a fragment which binds...), unpredictability of and the lack of information in the prior art about residues of the 4-1BB

receptor which binds a 4-1BB ligand and especially about H4-1BB, particularly in view of the low sequence similarity between mouse and human 4-1BB, it would require undue experimentation to practice the claimed invention. The invention is not enabled.

Applicant argues that the need to carry out extensive screening to identify a particular compound does not constitute undue experiment. This statement taken alone is correct, however the issue of enablement relates to many factors in addition to the quantity of experimentation required to determine if an invention is enabled (see preceding paragraph).

Applicant argues rejections are based on the alleged failure to meet the written description requirement for fragments of SEQ ID NO:2. No rejections were made for lack of written description *per se*. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

With respect to claim 26, Applicant argues that a pharmaceutical composition comprising a soluble H4-1BB polypeptide which comprises the extracellular domain of SEQ ID NO:2 or fragment thereof will suppress T cell-dependent immune responses as described on pages 17-18 of the specification. First, Figures 5a-c described on pages 17-18 show a schematic of cells in which the normal interaction between 4-1BB and its ligand are blocked. No experiments are presented, and basis for the effect of blocking 4-1BB is hypothetical and based on the interaction of CD28 to its counter-receptor B7. Applicant's arguments (page 6, second paragraph) are based on the knowledge that 4-1BB is transcribed during T cell activation. Induction of transcription does not necessarily lead to T cell-dependent immune responses. Second, for the reasons of record, there is a lack of enablement of a pharmaceutical because it carries the requirement of being enabled for treatment. The current application does not provide a reasonable expectation that the claimed composition could be used to treat due to the absence of guidance and information presented in the specification and prior art. It is suggested that if claims to a composition are desired, a claim

such as "a composition comprising the polypeptide of claim 24 and a suitable diluent", would not raise the points currently at issue for a pharmaceutical composition.

The argument that one would be capable of determining whether a disease is associated with a T cell, is not persuasive. The pharmaceutical composition is not enabled for the reasons of record and as rephrased here, namely there is a lack of guidance about and examples of which diseases associated with T cells can be treating by affecting 4-1BB; the claims are broad; there is a lack of predictability (see above); and it would require undue experimentation to identify a representative number of diseases/conditions which the claimed pharmaceutical could be used to treat.

Claim Rejections - 35 USC § 103

Response to Amendment

2. The Declaration filed on Oct. 30, 1998 under 37 CFR 1.131 has been considered but is ineffective to overcome the Schwarz et al. reference.

The evidence submitted is insufficient to establish a conception of the invention prior to the effective date of the Schwarz et al. reference. While conception is the mental part of the inventive act, it must be capable of proof, such as by demonstrative evidence or by a complete disclosure to another. Conception is more than a vague idea of how to solve a problem. The requisite means themselves and their interaction must also be comprehended. See *Mergenthaler v. Scudder*, 1897 C.D. 724, 81 O.G. 1417 (D.C. Cir. 1897). The Declaration is insufficient for the following reasons: First, there is an insufficient showing of conception. Conception in this case would require a showing that the inventor conceived of at least as much as the reference showed. The reference shows the full-length protein and nucleic acid sequences. Applicant says in section 4 of the Declaration that "Prior to the April 22, 1993 publication date of Schwarz et al., I had isolated and purified a portion of a human 4-1BB gene...." Since only a portion was isolated, this is not as much as the reference shows, which is the full-length cDNA. Second, even

if the declaration suggested complete conception before the publication of Schwarz, there is insufficient proof. The copy of the autoradiogram presented as evidence is entirely black with no visible band. Further, there is no information on the autoradiogram to explain what the hypothetical band was identified as (*i.e.*, a portion of H4-1BB) to show that at the time it was made, Applicant was aware of what he was in possession of.

3. Applicants argue that the Ayala reference does not point to the invention claimed. The fact that Ayala et al. et al. does not suggest preparation of the polypeptide having the sequence of SEQ ID NO:2 or a fragment thereof, does not diminish the appropriate reliance on the reference in the obviousness rejection. By Ayala et al. et al. stating that many, and possibly all, gene have multiple alleles, the artisan of ordinary skill would have reasonably expected that 4-1BB (ILA) was no exception and was represented by multiple alleles.

Conclusion

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Friday from 8:00AM to 4:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached at (703) 308-2731.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

cmk
November 18, 1998

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER